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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,377	04/07/1999	ROBERT J. D'AMATO	05213-0272	6240

7590 06/13/2005

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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/287,377	D'AMATO, ROBERT J.	
	Examiner	Art Unit	
	Dwayne C. Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22FEB2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12,21-28,32-39,43,44 and 47-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-12,21-28,32-39,43,44 and 47-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 7-12, 21-28, 32-39, 43, 44, and 47-54 are pending.

2. Claims 7-12, 21-28, 32-39, 43, 44, and 47-54 are rejected.

3. Claims 1-6, 13-20, 29-31, 40-42, and 45-46 are cancelled.

Response to Arguments

4. Applicant's arguments filed February 22, 2005 have been fully considered but they are not persuasive. Applicants present the following arguments. First, applicant submits that the pending claims are enabled because the specification "contains a teaching of the manner and process of making and using and invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented. Second, applicant disagree with the Office's allegation that the specification fails to provide sufficient guidance for those of ordinary skill in the art because "a disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the methods will fall within the scope of a claim and will possess the alleged activity." Third, applicant submits that no undue experimentation is necessary to practice the claimed invention. Fourth, applicants allege that the instant specification provides sufficiently detailed disclosure for those of skilled in the art to conclude that the inventor had possession of the claimed invention. Fifth, applicants assert that the claim limitations are not met by the prior art reference of Billson et al. Sixth, applicants contend that the Office has not provided the requisite

support for their contention that the skilled artisan would have been motivated to utilize agents other than thalidomide as well as its derivatives in pharmaceutical compositions. Seventh, applicants assert that the Office has improperly used the "obvious to try" legal principle. Eighth, applicants next argue that one having ordinary skill in the art would not have been motivated to combine Little et al. with Billson et al. Ninth, applicants submit that the cyclic imide formation allegedly disclosed in Solomons involves a primary amine, while one of the hydrogens in the amine groups present in compounds P, Q, R, and S is replaced with a bulky chemical moiety, which would hinder the formation of the cyclic imide.

5. First, applicant submits that the pending claims are enabled because the specification "contains a teaching of the manner and process of making and using and invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented. However, the instant specification is only enabled for the angiogenesis inhibiting compounds that could be employed in this invention other than thalidomide, EM-12, PGA, PG Acid and supidimide along with sulindac *and only for* the treatment of the diseases of corneal neovascularization and Crohn's Disease, and V2-carcinoma, (see pages 33-40 of the instant specification), does not reasonably provide enablement for "inhibiting angiogenesis" and "treating angiogenesis dependent disease". The specification does not provide guidance, direction and support for the coverage of the broad terms of "inhibiting angiogenesis" and "treating angiogenesis dependent disease".

6. Second, applicant disagree with the Office's allegation that the specification fails to provide sufficient guidance for those of ordinary skill in the art because "a disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the methods will fall within the scope of a claim and will possess the alleged activity." There is no clear guidance and direction to enable the skilled artisan to make and use every functional compound of for example claim 7 that is further combined with the litany of compounds that are embraced by the functional recitation of anti-inflammatory drug, such as steroid and NSAID and moreover to treat the laundry list of ailments that are embraced by the broad functional recitation of "angiogenesis dependent disease", such as the numerous ailments of claim 28. In addition, the instant specification only has support for the angiogenesis inhibiting compounds that could be employed in this invention other than thalidomide, EM-12, PGA, PG Acid and supidimide along with sulindac *and only for* the treatment of the diseases of corneal neovascularization and Crohn's Disease, and V2-carcinoma, (see pages 33-40 of the instant specification), does not reasonably provide enablement for "inhibiting angiogenesis" and "treating angiogenesis dependent disease".

7. Third, applicant submits that no undue experimentation is necessary to practice the claimed invention. The instant specification is only enabled for the angiogenesis inhibiting compounds that could be employed in this invention other than thalidomide, EM-12, PGA, PG Acid and supidimide along with sulindac *and only for* the treatment of the diseases of corneal neovascularization and Crohn's Disease, and V2-carcinoma,

(see pages 33-40 of the instant specification), does not reasonably provide enablement for "inhibiting angiogenesis" and "treating angiogenesis dependent disease".

8. Fourth, applicants allege that the instant specification provides sufficiently detailed disclosure for those of skilled in the art to conclude that the inventor had possession of the claimed invention. However the definitions of angiogenic dependent diseases or angiogenic associated diseases are not definitive, and do not provide the artisan with précised definitions and meanings that are embraced by the functional recitations of angiogenic dependent or angiogenic associated diseases.

9. Fifth, applicants assert that the claim limitations are not met by the prior art reference of Billson et al. The prior art reference of Billson et al. clearly and specifically teach of administering thalidomide and a steroid, namely triamcinolone acetonide is used to treat macular degeneration, (see page 4, lines 11-19) as do the instant claims. The skilled artisan is provided with clear motivation to make a composition that is comprised of thalidomide and a steroid as well as methods of using these compositions to treat the claimed ailment, such as macular degeneration, as evidenced from the teachings of Billson et al.

10. Sixth, applicants contend that the Office has not provided the requisite support for their contention that the skilled artisan would have been motivated to utilize agents other than thalidomide as well as its derivatives in pharmaceutical compositions. It is surely within the level of the skilled artisan to utilize derivatives and analogues of a compound such as thalidomide as long as the inherent properties of a given compound, such as thalidomide, are not materially changed. Accordingly, it would have been

obvious to one having ordinary skill in the art to include various iterations and derivatives of known compounds when the prior art teaches that a compound, namely thalidomide, is used to treat the very same ailment, such as macular degeneration, that is claimed. Moreover, applicant requests documentation of well-known cyclization reactions between carboxylic acids and carboxylic acid amide functional groups. Lactones are carboxylic acids that have hydroxyl groups on a gamma or delta carbon atom (3 or 4, respectively carbons away from the carboxylic acid moiety group), which may undergo intramolecular esterification to give a cyclic ester, (see pages 799-800 of Solomons, 3rd Edition, Organic Chemistry, 1986). Likewise, lactams are structurally related to lactones with the exception of having an internal carboxylic acid amidyl moiety in lieu of the carboxylic acid ester moiety as in a lactone, (see pages 799, 800, and 806 of Solomons, 3rd Edition, Organic Chemistry, 1986). Consequently, compounds with carboxylic acids that have amino groups on a gamma or delta carbon atom would also undergo intramolecular cyclization reactions, thus generating lactams. In addition, various iterations of carboxylic acids and its corresponding derivatives, namely amides, anhydrides, halides, can readily undergo internal cyclization reactions as the distance between carboxylic acid functional group increases between a functional groups such as hydroxyl, amino, or another carboxylic acid moiety, (for instance see page 802 cyclic anhydrides are reacted with ammonia or an amine while heating to generate cyclic imides). Accordingly, internal cyclization reactions are clearly obvious to one having ordinary skill in the art as evidenced by Solomons, 3rd Edition, Organic Chemistry, 1986. Even though the instant claims may exclude the compound of thalidomide one having

ordinary skill in the art has the knowledge to generate and recognize derivatives and precursors of compounds through basic organic chemistry. Compounds such as P, Q, R, or S could readily undergo internal cyclization reactions under the right conditions, and the skilled artisan would readily discern and recognize precursors of such compounds as obvious variants of a known compound, especially the very well known compound of thalidomide.

11. Seventh, applicants assert that the Office has improperly used the "obvious to try" legal principle. However, the prior art reference of Billson et al. clearly and specifically teach of administering thalidomide and a steroid, namely triamcinolone acetonide is used to treat macular degeneration, (see page 4, lines 11-19) as do the instant claims. The skilled artisan is provided with clear motivation to make a composition that is comprised of thalidomide and a steroid as well as methods of using these compositions to treat the claimed ailment, such as macular degeneration, as evidenced from the teachings of Billson et al. Accordingly, the broad functional terms of the instant invention are under 35 U.S.C. 103(a) as again rendered obvious as being unpatentable over Billson et al. of WO 95/03807 is maintained for reasons cited previously and here.

12. Eighth, applicants next argue that one having ordinary skill in the art would not have been motivated to combine Little et al. with Billson et al. Ninth, applicants submit that the cyclic imide formation allegedly disclosed in Solomons involves a primary amine, while one of the hydrogens in the amine groups present in compounds P, Q, R, and S is replaced with a bulky chemical moiety, which would hinder the formation of the

cyclic imide. As stated above in paragraph 10 of this Office Action, the skilled artisan is has the necessary knowledge and skill level to make and recognize derivatives and analogs of already known compounds, such as thalidomide. In addition, the skilled artisan could readily and easily make derivatives of thalidomide, which would obviously include uncycilized moieties of between the carboxylic acid functional group and a functional group such as a hydroxyl, amino, or another carboxylic acid moiety, as is instantly claimed. The cyclization reaction in compound Q would obviously occur with the primary amino group and the acyclic carboxylic acid group whereas the cyclization reactions of compounds P and R would obviously occur with the two acyclic carboxylic acid moieties because compounds with carboxylic acids that have amino groups on a gamma or delta carbon atom would also undergo intramolecular cyclization reactions, thus generating lactams. In addition, various iterations of carboxylic acids and its corresponding derivatives, namely amides, anhydrides, halides, can readily undergo internal cyclization reactions as the distance between carboxylic acid functional group increases between a functional groups such as hydroxyl, amino, or another carboxylic acid moiety, (for instance see page 802 cyclic anhydrides are reacted with ammonia or an amine while heating to generate cyclic imides).

Claim Rejections - 35 USC § 112

13. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

14. The rejection of claims 7-12, 21-28, 32-39, 43, 44, and 47-54 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treating the diseases of corneal neovascularization and Crohn's Disease, and V2-carcinoma, does not reasonably provide enablement for "inhibiting angiogenesis" and "treating angiogenesis dependent disease" is maintained for both the above stated and reasons of record.

15. The rejection of claims 27, 28, 37-39, and 48-54 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained and repeated. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained. There is insufficient descriptive support for the phrase "treating angiogenesis dependent disease". In addition, the instant specification does not describe what is meant by the phrase "treating angiogenesis dependent disease". Structural identifying characteristics of the phrase "treating angiogenesis dependent disease". There is no evidence that there is any per se structure/function relationship between the phrase "treating angiogenesis dependent disease". The instant specification does provide an adequate written description for the phrase "treating angiogenesis dependent disease". Accordingly, these claims fail to comply with the written description requirement.

16. The rejection of claims 15, 19, 20, 45, and 46 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is removed in response to the cancellation of these claims of February 22, 2005.

Claim Rejections - 35 USC § 103

17. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

18. The rejection of claims 7-12, 21-28, 32-39, 43, 44, and 47-54 under 35 U.S.C. 103(a) as being unpatentable over Billson et al. of WO 95/03807 is maintained for reasons cited previously and above.

19. The rejection of claims 7-12, 21-28, 32-39, 43, 44, and 47-54 under 35 U.S.C. 103(a) as being unpatentable over Billson et al. of WO 95/03807 in view of Little, II et al of U.S. Patent No. 5,348,942 is also maintained for both the above-stated and reasons of record.

20. The rejection of claims 9-12 under 35 U.S.C. 103(a) as being unpatentable over Billson et al. of WO 95/03807 in view of Little, II et al of U.S. Patent No. 5,348,942 is maintained for the reasons of record and those stated above.

Obviousness-type Double Patenting

21. The provisional rejection of claims 7-12, 21-28, 32-39, 43, 44, and 47-54 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 09/480,448 is maintained.

22. The provisional rejection of claims 1, 7-12, 15, 19-28, 32-39, and 43-48 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 10/430,892 is maintained.

Conclusion

23. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-

0578. The examiner can normally be reached on Mondays, Tuesdays, Wednesdays, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, may be reached at (571) 272-0951. The official fax No. for correspondence is (571)-273-8300.

Also, please note that U.S. patents and U.S. patent application publications are no longer supplied with Office actions. Accordingly, the cited U.S. patents and patent application publications are available for download via the Office's PAIR, see http://pair-direct.uspto.gov. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 1-866-217-9197 (toll free).

DWAYNE JONES
PRIMARY EXAMINER
Tech. Ctr. 1614
June 9, 2005